

Deep Insight Section

Angiogenic factors and cancer therapy

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Abstract

Tumor growth and metastasis are dependent on neovascularization, which is mainly accomplished by the process of angiogenesis-sprouting of new microvessels from the existing blood vessels. To gain its ability of growth and invasiveness, malignant cells often express high levels of angiogenic factors that stimulate tumor angiogenesis and remodel tumor vessels. In addition to malignant cells, other host cells in the tumor microenvironment, including inflammatory cells, stromal fibroblasts and perivascular cells also significantly contribute to production of angiogenic factors and cytokines. Co-existence of various angiogenic factors and cytokines will inevitably cause interplay of various signaling pathways, leading to synergistic effects of tumor angiogenesis. Thus, therapeutic development of angiogenic factor inhibitors should be aimed to block not only the vertical signaling pathway triggered by a specific factor, but the horizontal interplay of various angiogenic pathways. This review discusses the mechanisms that underlie tumor angiogenesis, provides a few examples of angiogenic pathways that are commonly seen in most tumor types, and discusses the challenges of antiangiogenic cancer therapy.

Key words

Angiogenesis, vasculature, growth factors, cancer, metastasis

Discovery of tumor angiogenic factors

In 1971, Judah Folkman, in his hypothetical and conceptual article, proposed that tumors produce angiogenic factors and inhibition of tumor angiogenesis would offer a new therapeutic option for treatment of cancer (Folkman, 1971). Based on this hypothesis, extensive research was initiated during early research for identification of tumor-derived-angiogenic factors and accumulating evidence supported the existence of tumor angiogenic factors although their identities remained unknown at that time (Folkman et al., 1971; Langer et al., 1976). The first angiogenic factor was isolated from the pituitary of mammals (Gospodarowicz, 1976). In 1984, Folkman and colleagues isolated the first tumor angiogenic factor, i.e., basic fibroblast growth factor (bFGF or FGF-2), from a chondrosarcoma, and thus

validating the concept that tumors produce angiogenic factors to induce neovascularization (Shing et al., 1984). Simultaneous to identification of tumor angiogenic factors, Dvorak and colleagues identified a potent vascular permeability factor (VPF) from tumor cells (Senger et al., 1983). These initial findings demonstrated that tumor-derived angiogenic factors are able to stimulate angiogenesis and to modulate vascular structures. The same VPF, clones sequenced by Connolly and colleagues, was found to be structurally related to platelet-derived growth factor (Keck et al., 1989). In the same issue of Science magazine, Dr. Napoleone Ferrara and colleagues published their findings on identification of vascular endothelial growth factor (VEGF) as a potent angiogenic factor, which sequence identity with VPF (Leung et al., 1989). These initial findings paved new avenues for subsequent identification and cloning of numerous other angiogenic factors related to tumor growth and invasion, including those members in the VEGF, FGF, PDGF, angiopoietin, and notch ligand families.

Tumor microenvironment and the switch to an angiogenic phenotype

Genetic instability of malignant cells often leads to accumulation of mutations of oncogenes and tumor suppressor genes and these mutated oncogenic proteins often upregulate expression levels of angiogenic factors (Cao et al., 2009). The fact that tumor tissues contain heterogenic populations of malignant cells implies that various tumor cells even in the same tumor mass would produce different levels of angiogenic factors. Although the clinical significance of highly angiogenic tumor cells in tumor growth and invasion is not fully understood, it is reasonably speculated that the highly angiogenic tumor cell population might eventually dominate the entire tumor mass owing to their growth advantages. In contrast to tumor cells, somatic cells in healthy adult tissues may only produce modest levels of proangiogenic factors, which are not able to induce an angiogenic phenotype. Additionally, endogenous angiogenesis inhibitors are predominately expressed at high levels to prevent excessive neovascularization (Cao, 2008). Thus, angiogenesis rarely occurs in healthy adult tissues, except in the reproductive organs and tissue regeneration. To create an angiogenic phenotype, tumors have to tip the balance of angiogenic factors over inhibitors (Figure 1). Other cell types in the tumor microenvironment including inflammatory cells and stromal fibroblasts are also significant sources of tumor angiogenic factors and

they significantly contribute to the switch of tumor angiogenesis (Figure 1).

Angiogenic signaling pathways

Since identification of VEGF and FGF-2 as potent angiogenic factors in 1980s, numerous angiogenic pathways have been discovered and their specific roles in regulation of tumor angiogenesis and vascular remodeling have been defined. Most angiogenic factors trigger angiogenic signals through specific interaction with their cell surface receptors that often contain tyrosine kinase domains in endothelial cells.

In general, various angiogenic factors appear to have distinct functions in regulation of vessel growth, vascular permeability and remodeling. VEGF is a potent angiogenic and vascular permeability factor that induces vascular sprouting and vascular leakiness (Leung et al., 1989; Senger et al., 1983). The Dll4-Notch signaling system prevents excessive vascular sprouting from the "stalk region" of blood vessels (Noguera-Troise et al., 2006; Ridgway et al., 2006) (Figure 2). The PDGF-BB-PDGFR- β signaling in perivascular cells such as pericytes mediates recruitment of these mural cells onto the newly formed vasculatures (Lindahl et al., 1997). These distinctive functions can be divided even within the same family angiogenic factors. For example, Ang1 and Ang2 within the angiopoietin family seem to display opposing effects on vascular remodeling even though they bind to the same endothelial Tie2 receptor (Maisonpierre et al., 1997).

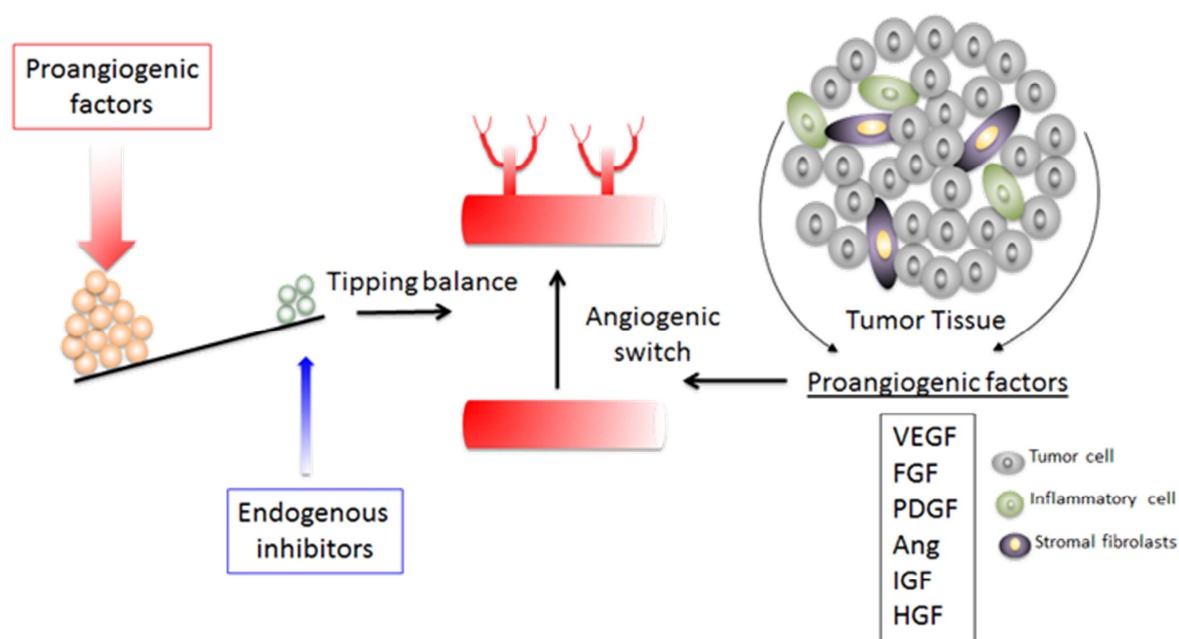


Figure 1. Angiogenic switch in tumor tissues. Tumor cells together with other host cells including inflammatory cells and stromal fibroblasts produce high levels of proangiogenic factors and reduced levels of endogenous inhibitors, tipping the balance towards a proangiogenic phenotype.

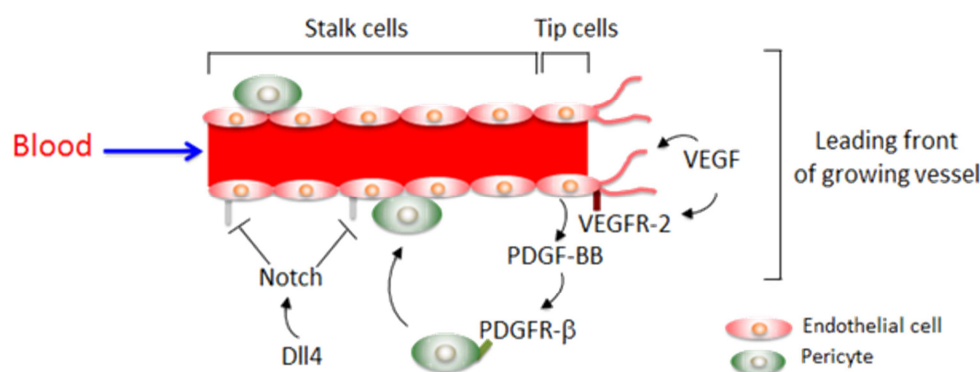


Figure 2. Angiogenic regulators that control the precise steps of new vessel growth. VEGF is a driving force that induces tip cell formation through activation of VEGFR2 signaling. Angiogenic endothelial cells produce PDGF-BB to recruit pericytes onto newly formed vessels to prevent excessive sprouting. The Dll4-Notch1 signaling also prevent excessive vascular sprouting from "stalk cells".

Thus, angiogenic factors whether within the same family or in different families have distinctive roles in modulation of vessel growth and remodeling. During tumor angiogenesis, these signaling pathways may become uncoordinated, leading to the formation of disorganized and primitive vascular networks.

Interplay between angiogenic factors

Co-existence of various angiogenic factors, cytokines, signaling receptors and intracellular signaling components often results in crosstalk between various signaling pathways. Thus, in tumor tissues various angiogenic factors and cytokines not only transduce their signals vertically, but also interact each other horizontally. At the ligand level, various angiogenic factors with the same family can interact each other. For example, VEGF-A and PlGF or VEGF-B can form heterodimers in addition to their respective homodimers and heterodimers may different biological functions (Cao et al., 1996; Olofsson et al., 1996). Similarly, PDGF-A and PDGF-B can also form heterodimers that display overlapping but yet different functions from their corresponding homodimers (Heldin and Westermark, 1989b). The same heterodimerization mechanism also exists in various VEGF receptor molecules and PDGF receptor molecules (Heldin and Westermark, 1989a; Mac Gabhann and Popel, 2007). Similarly, interactions between cell surface receptors beyond the same family also exist, demonstrating the complex signaling transduction of these receptors. Activation of a particular signaling pathway often induces and amplifies signaling pathways. For example, stimulation of endothelial cells and angiogenesis by FGF-2 induces expression levels of PDGFR expression, and thus triggering a synergistic angiogenic response (Cao et al., 2003). Such a synergistic angiogenic activity in the tumor microenvironment promotes tumor growth, invasion and metastasis

(Nissen et al., 2007). Therefore, assessment of angiogenic profiles in a given tumor tissue should consider potential interaction relations between various angiogenic factors and signaling pathways.

Targeting angiogenic pathways in tumors

The original idea of blocking tumor-derived angiogenic factors for cancer therapy was raised by Dr. Judah Folkman. In his conceptual paper, Folkman wrote "One approach to the initiation of 'anti-angiogenesis' would be the production of an antibody against tumor angiogenic factor" (Folkman, 1971). His prediction and vision were validated in human cancer patients 33 years later with approval of bevacizumab, an anti-VEGF neutralizing antibody, by US FDA in 2004 for treatment of human colorectal cancer (Hurwitz et al., 2004). In fact, bevacizumab remains as the most commonly used antiangiogenic drugs for treatment of various human cancers either in combination with chemotherapy or monotherapy settings. Antiangiogenic drugs that block signaling pathways can be divided into several categories according to their targets and specificity: 1) Inhibition of angiogenic factor production from various cell types of tumors. These may include inhibition of transcription and translation of a specific angiogenic factor; 2) Functional neutralization of angiogenic factors. Bevacizumab targeting VEGF is one of such neutralizing antibodies (Hurwitz et al., 2004); 3) Anti-receptor neutralizing antibodies. Similar to angiogenic ligands, binding of antibodies to specific regions of extracellular domains of a receptor could also effectively block their ligand-triggered angiogenic signaling. Ramucizumab, an anti-VEGFR2 neutralizing antibody is an example of such drugs that are under clinical development (Fuchs et al., 2014); 4) Tyrosine kinase inhibitors (TKIs) that block angiogenic receptor functions. There are 7 currently US-FDA-approved antiangiogenic TKIs, including: axitinib,

cabozantinib, pazopanib, regorafenib, sorafenib, sunitinib, and vandetanib (Choueiri et al., 2012; Cohen et al., 2008; Escudier et al., 2007; George et al., 2012; Houvras and Wirth, 2011; Motzer et al., 2013; Motzer et al., 2007). In general, TKIs lacks specificity and each TKI blocks the activity of several tyrosine kinases. The antiangiogenic TKIs share overlapping, but yet target different spectrums of angiogenic pathways. VEGFR2, as a key functional receptor for VEGF-induced angiogenesis, is one of the common targets of these TKIs. TKIs have been clinically used for treatment of various human cancers; 5) Inhibition of downstream signaling components. For example, mTOR (mammalian targets of rapamycin) inhibitors including temsirolimus and everolimus potently suppress tumor angiogenesis (Fazio et al., 2007; Yao et al., 2011); 6) Generic angiogenesis inhibitors. Thalidomide is an example of generic angiogenesis inhibitor that blocks a common pathway of angiogenesis that is currently used for treatment of multiple myeloma (Singhal et al., 1999); 7) Endogenous angiogenesis inhibitors. These inhibitors such as angiostatin and endostatin exhibit a broad-spectrum inhibitory activity against tumor angiogenesis induced by various stimuli (O'Reilly et al., 1997; O'Reilly et al., 1994). A variant version of endostatin has been approved by the Chinese FDA for treatment of lung cancer in human patients (Han et al., 2011).

Despite successful development of these drugs for treatment of human cancers, the survival beneficial effects, in general, are rather modest for most cancer types. A majority of cancer patients show intrinsic resistance toward these antiangiogenic drugs (Cao and Langer, 2008, 2010). For those patients who initially respond to antiangiogenic drugs can also develop evasive refractoriness. Additionally, antiangiogenic drugs also produce various side effects in cancer patients. Given the essential roles of VEGF in regulation of human physiology, it is perhaps not unexpected to observe broad side effects of anti-VEGF-based antiangiogenic drugs in human patients.

Lymphangiogenic factors and therapeutic targets

Tumor-produced angiogenic factors not only stimulate angiogenesis, but often induce lymphangiogenesis, which significantly contribute to lymph node metastasis (Cao, 2005). Similar to blood vessel angiogenesis, tumor lymphangiogenesis is also regulated by multiple growth factors. Members in the VEGF, FGF, PDGF, Ang, HGF, and IGF families have been found to actively participate in regulation of lymphangiogenesis (Cao, 2005). Moreover, these factors induce intra- and peri-tumoral lymphangiogenesis that facilitate lymphatic

metastasis. Among these known lymphangiogenic factors, the VEGF-C-VEGFR3 signaling system is probably the most well characterized signaling pathway in regulation of physiological and pathological lymphangiogenesis (Adams and Alitalo, 2007; Stacker et al., 2002). VEGFR3 seems to be exclusively expressed on lymphatic endothelial cells although it is also found in angiogenic endothelial cells (Tammela et al., 2008). Several lymphangiogenic factors indirectly induce lymphangiogenesis through activation of the VEGF-C-VEGFR3 signaling system. This indirect regulatory mechanism occurs at both VEGF-C ligand and VEGFR3 receptor levels at which other factors often upregulate expression of these two signaling molecules. Notably, the VEGFR3-mediated lymphatic endothelial tip cell formation is probably essential for other lymphangiogenic factor-induced lymphangiogenesis. For example, FGF-2-induced lymphangiogenesis requires the VEGFR3 signaling system for sprouting and inhibition VEGFR3 completely ablates FGF-2-induced lymphangiogenesis (Cao et al., 2012). Given the essential role of lymphangiogenesis in cancer metastasis, inhibition of lymphangiogenesis would in principle be a valid approach for anti-metastatic cancer therapy. However, development of drugs to block cancer metastasis for clinical use remains a challenging issue and pharmaceutical companies remain reluctant to pursue this avenue.

Mechanistic challenges of antiangiogenic cancer therapy

The initial antiangiogenic concept for treatment of cancer raised by Judah Folkman has led to successful development of antiangiogenic drugs for treatment of various human cancers. Despite the fact that the growth of all solid tumors is dependent on angiogenesis, the response rate of antiangiogenic therapy in human cancer patients is rather modest (Cao and Langer, 2010; Kerbel, 2008). In most types of cancers, antiangiogenic drugs are delivered together with chemotherapeutics or in combination with other therapeutic modalities and antiangiogenic monotherapy produce insignificant improvement of patient survivals. This clinical finding is in marked contrast to the treatment regimen in preclinical tumor models in which most antiangiogenic agents show potent antitumor effects when delivered as a single agent. Why would human and mouse tumors respond so differently to the same drug (Cao, 2011)? This important question remains unresolved at this time of writing. One of challenging issues of translating preclinical findings into clinical practice is the relevance of preclinical mouse tumor models to human patients. In mouse tumor models, we often use genetically identical mice to study the effect of a given antiangiogenic agent whereas each human cancer patient carries

genetic information that is different from others. Tumors in human patients contain different mutations of crucial genes related to cell growth and oncogenesis whereas mouse tumors are often identical from the same cell line. Human cancers are treated at different stages of malignant progression and mouse tumors are often treated at the same time and similar size during cancer development. Importantly, in mouse tumor models therapeutic efficacy of antiangiogenic drugs is assessed by measuring tumor size and beneficial effects of antiangiogenic therapy are often determined based on survival improvement. During clinical practice, it is increasingly noticed that tumor size cannot be used as a reliable surrogate marker to predict survival benefits and antiangiogenic therapy. Another important issue is the mechanism that underlies combination therapy, which remains unknown.

A couple of hypotheses have been proposed to explain therapeutic benefits underlying the combination of antiangiogenic drugs with chemotherapeutics.

Anti-angiogenic drug-induced vascular normalization modulates chemotherapeutic delivery in tumor tissues offers an attractive mechanism for explaining the beneficial effects of combination therapy (Jain, 2005).

Despite some interesting findings in mouse tumor model, the vascular normalization concept needs to be validated in human cancer patients (Van der Veldt et al., 2012). Another interesting concept is that antiangiogenic drugs significantly reduce chemotherapy-related toxicity in cancer hosts (Zhang et al., 2011).

Again, this interesting concept warrants clinical validation. Taken together, the mechanisms by which antiangiogenic drugs improve survivals of cancer patients remains an enigma despite these drugs suppress tumor angiogenesis. Future preclinical and clinical studies should focus on mechanisms that underlie clinical benefits of these drugs in cancer patients.

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